

Attitude by the Reviewer

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Re: defense of dissertation for acquisition of scientific degree “Doctor of Science” the Professional field 4.3. Biological Sciences, specialty “molecular biology” in the Roumen Tsanev Institute of Molecular Biology, Bulgarian Academy of Sciences

Author: Professor Iva Ugrinova Zlatkova, PhD in IMB-BAS

Title: Common target, different agents: fundamental vulnerabilities of the tumor cell as a basis for selective antitumor action

Brief presentation of the author of the DSc dissertation

Prof. Iva Ugrinova graduated in 1992 with a Master's degree in biotechnology with a specialty in "Genetic and Cellular Engineering" at the Faculty of Biology of Sofia University "St. Kliment Ohridski". Her scientific career at IMB-BAS began in 1995, where in 2002 she obtained an educational and scientific degree "doctor" in the specialty "molecular biology" at IMB-BAS on the topic: "Post-synthetic acetylation of the non-histone protein HMGB1 - characterization and DNA binding properties". She quickly moved through the successive stages of academic growth. She was elected as an associate professor in 2011, and in 2019 - as a professor of molecular biology. Since 2013 she has been the Head of the "Chromatin Structure and Function" section at IMB. She held the position of Director of the IMB for two consecutive mandates (2014-2022), and is currently the Deputy Director of the Institute. She had two post-doctoral specializations (2004-2005 and 2007) at the École normale supérieure de Lyon, Lyon, France, where she was subsequently invited professor (2008 and 2014). Currently, Prof. Ugrinova is a project leader and participant in two other projects funded by the Bulgarian National Science Foundation in the field of the dissertation topic and are focused on the development of new anti-cancer drugs. She led the IMB Work Package at the National Research Center of the Ministry of Education and Science "BioActiveMed" (2018-2023). She is a participant in an ongoing project funded under the Horizon Europe Framework Program on the topic “Advanced epigenetics studies to increase the research and innovations capacity of the Roumen Tsanev Institute of Molecular Biology of the Bulgarian Academy of Sciences (AEGIS-IMB)". Prof. Ugrinova has published 92 articles, of which 87 with impact factor or impact rank, that generate over 2349 citations and h-index 22. During the last 5 years, she has 36 articles with IF and 1000 citations, which distinguishes her as an active scientist with international recognition. In the current dissertation work for the degree of "Doctor of Sciences" she has applied 10 articles

Timeliness and aims of the DSc dissertation

The author of the dissertation, Prof. Iva Ugrinova, has dedicated her long term scientific carrier to the role of non-histone proteins-HMGB1/2 in epigenetic regulation, DNA repair, programmed cell death and oncogenesis. A main part in Prof. Ugrinova's research is the factors involved in

genomic stability and cell signaling with crucial importance for cell fate (survival or death) in the context of pathological processes related to carcinogenesis and metastasis. This topic is of fundamental importance with broad prospects for clinical application in the field of oncopharmacology in the aspect of developing new synthetic and natural drugs for selective and targeted therapy of cancer diseases. In this direction, the research of Prof. Ugrinova over the past 5 years has marked significant progress not only in the synthesis of new effective anticancer compounds, but also in obtaining new knowledge in the mechanism of their selective action on cancer cells. The literature review of the dissertation work is fascinatingly written and directly addressed to the topic of the dissertation. In the sections of the review, along with the critical review of the literature data, the author has concisely and briefly incorporated the main research aspects of her work and her own contributions regarding the mechanism of action of the newly developed anticancer agents. This elegant approach allows us to gain an idea of the meaning, significance and innovative nature of the dissertation work from the very beginning. It consists in developing a concept of the common vulnerabilities of the tumor phenotype to new anticancer agents, that are promising for the development of a modern effective strategy for the selective therapy of oncological diseases.

In this aspect, Prof. Ugrinova formulates the goal of the present dissertation work to reveal the general molecular mechanisms of new highly selective antitumor agents of synthetic and natural origin, based on a limited number of fundamental vulnerabilities of cancer cells. In an applied aspect, the author aims to develop an approach to increase their pharmaceutical applicability through modern polymer nanosystems. She formulates 5 tasks, specified to the mechanism of the antitumor action of different types of compounds and identification of the common fundamental vulnerabilities of the tumor cell (oxidative and replication stress, DNA damage, activation of programmed cell death/apoptosis). The goals and tasks fully correspond to the topic of the dissertation work.

Results, discussion and scientific contribution of the DSc dissertation

In general, the dissertation work is structured in an unconventional way with separate sections "Materials and Methods", "Results and Discussion". Instead, the publications used are presented and attached, which gives the advantage of direct information with the author's original data, on the one hand, and the relevance of the approaches and methods used to generate the original results and scientific achievements.

The current dissertation investigates five classes of agents, each of which attacks one or more of the fundamental vulnerabilities of tumor cells - ferrocene-containing camphor sulfonamides, acting through redox activity and induction of oxidative stress; heterocyclic-annulled naphthalimides - as DNA-targeting inducers of replication stress; bioactive substances from the hemolymph of the marine mollusk *Rapana venosa* - with a p53-dependent and immunomodulatory profile; natural products of plant and fungal origin (cannabidiol, mushroom extracts and *Croton lechleri*) - with convergent apoptotic mechanisms; and polymeric nanosystems, which serve as a tool for controlled delivery and improvement of the therapeutic profile of chemical compounds.

The dissertation for “Doctor of Science” degree includes 10 publications published in world-renowned journals with a total impact factor of 48.9. Eight articles were published in journals with a quartile of Q1, 1 with Q3 and 1 with Q4. In total, they give 227 points on the G indicator, which exceeds twice the required 100 points. A list of 87 citations of these articles is presented, which generate 174 points out of the required 100 points. It is obvious that the total number of points exceeds the required minimum for the defense of a dissertation for Doctor of Science degree.

After presenting the publications in three sections of the results, a summary discussion was made, ending with a conclusion, scientific contributions, conclusions and prospective for future research by the author. 15 specific conclusions were presented, which directly correspond to the tasks of the dissertation work. Based on them, Prof. Ugrinova formulate the scientific contributions, according to their nature.

The fundamental contributions of dissertation is the finding the common limited vulnerabilities of tumor cells associated with disorders in redox homeostasis/oxidative stress, genomic stability/replication stress and mechanisms of cell survival/programmed cell death. The key role of the tumor suppressor factor p53 has been established in the realization of these pathological events. Thus, the author proves that the studied new agents exhibit the ability to affect preferentially tumor cells with relative sparing of normal cell populations.

The experimental contribution of the dissertation is characterization and elucidation of the molecular mechanism of the antitumor action of new synthetic compounds, such as ferrocene-camphor-sulfonamide derivatives and heterocyclic-annulled benzodioxin- and benzofuran-containing naphthalimides. The basis of their selective attack on tumor cells is the ability to modulate p53- and NF- κ B-dependent signaling pathways, as well as to induce oxidative and replication stress, irreversible DNA damage and subsequent apoptotic cell death. New data on the antitumor activity and mechanisms of action of natural products of animal (Black Sea *Rapana venosa*), plant and fungal origin are provided.

The applied contribution is the development of new biodegradable polymer nanosystems for the delivery of antitumor agents, providing improved solubility, stability and pharmaceutical applicability of biologically active compounds. This is an extremely promising direction, identified by Prof. Ugrinova in the context of developing a new generation of polymer nanocarriers for the combined delivery of siRNA and antitumor agents, applicable for targeted therapy.

Conclusion

The presented DSc dissertation work of Prof. Iva Ugrinova is the result of in-depth, interdisciplinary and high-tech scientific research of fundamental importance for cellular and molecular tumour biology, with high translational potential for medicine. They have received high international recognition as high-ranking in the world scientific literature. The author has developed an original concept that novel chemical agents and natural substances of diverse origin target a limited set of key molecular vulnerabilities of the tumour cell – oxidative and replication stress, DNA damage and programmed cell death with a central role of p53 in these

pathological events. Her current contributions and future research are extremely promising for the development of new strategies for effective selective and targeted therapy of oncological diseases.

All this gives me sufficient ground for excellent assessment of the dissertation thesis by Prof. Iva Ugrinova, entitled "Common target, different agents: the fundamental vulnerabilities of the tumor cell as a basis for selective antitumor action" and strongly recommend to the members of the Scientific Jury to vote positively for awarding of the scientific degree "Doctor of Sciences" to Prof. Ugrinova in the specialty "molecular biology" Professional field 4.3. "Biological Sciences".

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